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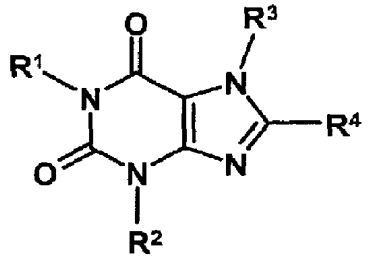
(54) DERIVES DE XANTHINE, LEUR PRODUCTION ET LEUR UTILISATION COMME MEDICAMENTS
(54) PHENACYL XANTHINE DERIVATIVES AS DPP-IV INHIBITOR

(57)

The invention concerns substituted xanthines of general formula (I), wherein: R1 to R4 are such as defined in Claim 1, and tautomers, stereoisomers, mixtures, prodrugs and salts thereof. Said compounds have advantageous pharmacological properties, in particular an inhibiting effect on the activity of the dipeptidyl peptidase IV (DPP-IV) enzyme.



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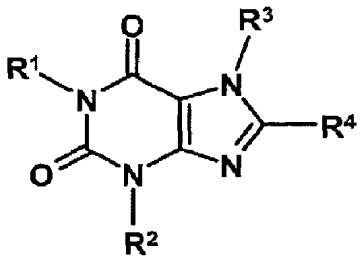
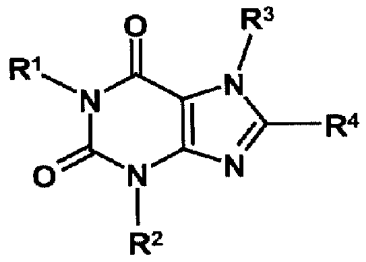


(I)

(57) Abrégé/Abstract:
The invention concerns substituted xanthines of general formula (I), wherein: R^1 to R^4 are such as defined in Claim 1, and tautomers, stereoisomers, mixtures, prodrugs and salts thereof. Said compounds have advantageous pharmacological properties, in particular an inhibiting effect on the activity of the dipeptidyl peptidase IV (DPP-IV) enzyme.

Abstract

The present invention relates to substituted xanthines of general formula



(I),

wherein R^1 to R^4 are defined as in claim 1, the tautomers, the stereoisomers, the mixtures, the prodrugs thereof and the salts thereof which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV).

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New xanthine derivatives, the preparation thereof and their use as pharmaceutical compositions

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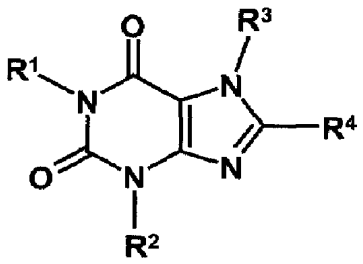
The present invention relates to new substituted xanthines of general formula



(I),

the tautomers, enantiomers, diastereomers, the mixtures thereof, the prodrugs thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV), the preparation thereof, the use thereof for the prevention or treatment of diseases or conditions associated with an increased DPP-IV activity or capable of being prevented or alleviated by reducing the DPP-IV activity, particularly type I or type II diabetes mellitus, the pharmaceutical compositions containing a compound of general formula (I) or a physiologically acceptable salt thereof as well as processes for the preparation thereof.

In the above formula I

R^1 denotes a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by R^{10} and R^{11}, where

R^{10} denotes a formylamino group,

a C_{3-7}-cycloalkyl-carbonylamino or C_{3-7}-cycloalkyl-C_{1-3}-alkyl-carbonyl-amino group,

a C_{6-9}-bicycloalkyl-carbonylamino or C_{6-9}-bicycloalkyl-C_{1-3}-alkyl-carbonylamino group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein

a methylene group is replaced by an oxygen or sulphur atom or by an imino, sulphinyl or sulphonyl group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2$ group is replaced by a –NH-CO or –NH-NH group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2-CH_2$ group is replaced by a –NH-CO-NH, –NH-CO-O or $-O-CH_2-O$ group,

a C_{6-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2-CH_2-CH_2$ group is replaced by a $-NH-CH_2-CH_2-NH$, $-NH-CO-CH_2-NH$, $-NH-CH_2-CH_2-O$, $-NH-CO-CH_2-O$ or $-O-CH_2-CH_2-O$ group,

a cycloheptyl-carbonylamino group wherein a $-CH_2-CH_2-CH_2-CH_2-CH_2$ group is replaced by a $-NH-CH_2-CH_2-CH_2-NH$, $-NH-CO-CH_2-CH_2-NH$, $-NH-CH_2-CH_2-CH_2-O$, $-NH-CO-CH_2-CH_2-O$ or $-O-CH_2-CH_2-CH_2-O$ group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein one or two methylene groups are replaced by carbonyl groups,

a C_{4-7}-cycloalkenyl-carbonylamino or C_{4-7}-cycloalkenyl-C_{1-3}-alkyl-carbonylamino group,

a C_{3-7}-cycloalkyl-sulphonylamino, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-sulphonylamino, arylsulphonylamino or aryl-C_{1-3}-alkyl-sulphonylamino group or

a heteroarylcarbonylamino group,

while the imino groups contained in the above mentioned groups may be substituted independently of one another by a C_{1-3}-alkyl group,

and R^{11} denotes a hydrogen, fluorine, chlorine, bromine or iodine atom

or

a C_{1-3}-alkyl, C_{1-3}-alkyloxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy or cyano group,

R^2 denotes a hydrogen atom,

a C_{1-6}-alkyl group,

a C_{2-4}-alkenyl group,

a C_{3-4}-alkynyl group,

a C_{3-6}-cycloalkyl group,

a C_{3-6}-cycloalkyl-C_{1-3}-alkyl group,

a tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl or tetrahydropyranylmethyl group,

an aryl group,

an aryl-C_{1-4}-alkyl group,

an aryl-C_{2-3}-alkenyl group,

an arylcarbonyl-C_{1-2}-alkyl group,

a heteroaryl-C_{1-3}-alkyl group,

a furanylcarbonylmethyl, thienylcarbonylmethyl, thiazolylcarbonylmethyl or pyridylcarbonylmethyl group,

a C_{1-4}-alkyl-carbonyl-C_{1-2}-alkyl group,

a C_{3-6}-cycloalkyl-carbonyl-C_{1-2}-alkyl group,

an aryl-D-C_{1-3}-alkyl group, while D denotes an oxygen or sulphur atom, an imino, C_{1-3}-alkylimino, sulphinyl or sulphonyl group,

a C_{1-4}-alkyl group substituted by a group R_a, where

> R_a denotes a cyano, carboxy, C_{1-3}-alkyloxy-carbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, di-(C_{1-3}-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

or a C_{2-4}-alkyl group substituted by a group R_b, where

> R_b denotes a hydroxy, C_{1-3}-alkyloxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl or 4-ethyl-piperazin-1-yl group and is isolated from the cyclic nitrogen atom in the 3 position of the xanthine skeleton by at least two carbon atoms,

R^3 denotes a C_{3-8}-alkyl group,

a C_{1-3}-alkyl group substituted by a group R_c, where

R_c denotes a C_{3-7}-cycloalkyl group optionally substituted by one or two C_{1-3}-alkyl groups,

a C_{5-7}-cycloalkenyl group optionally substituted by one or two C_{1-3}-alkyl groups,

an aryl group or

a furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl group, while the above mentioned heterocyclic groups may each be substituted by one or two C_{1-3}-alkyl groups or by a fluorine, chlorine, bromine or iodine atom or by a trifluoromethyl, cyano or C_{1-3}-alkyloxy group,

a C_{3-8}-alkenyl group,

a C_{3-6}-alkenyl group substituted by a fluorine, chlorine or bromine atom, or a trifluoromethyl group,

a C_{3-8}-alkynyl group,

an aryl group or

an aryl-C_{2-4}-alkenyl group,

and

R^4 denotes an azetidin-1-yl or pyrrolidin-1-yl group which is substituted in the 3 position by an amino, C_{1-3}-alkylamino or a di-(C_{1-3}-alkyl)amino group and may additionally be substituted by one or two C_{1-3}-alkyl groups,

a piperidin-1-yl or hexahydroazepin-1-yl group which is substituted in the 3 position or 4 position by an amino, C_{1-3}-alkylamino or a di-(C_{1-3}-alkyl)amino group and may additionally be substituted by one or two C_{1-3}-alkyl groups,

a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl moiety is additionally substituted by an aminocarbonyl, C_{1-2}-alkyl-aminocarbonyl, di-(C_{1-2}-alkyl)aminocarbonyl, pyrrolidin-1-yl-carbonyl, (2-cyano-pyrrolidin-1-yl)-carbonyl, thiazolidin-3-yl-carbonyl, (4-cyano-thiazolidin-3-yl)carbonyl, piperidin-1-ylcarbonyl or morpholin-4-ylcarbonyl group,

a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl moiety is additionally substituted in the 4 position or 5 position by a hydroxy or methoxy group,

a 3-amino-piperidin-1-yl group wherein the methylene group in the 2 position or 6 position is replaced by a carbonyl group,

a piperidin-1-yl or hexahydroazepin-1-yl group substituted in the 3 position by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, wherein in each case two hydrogen atoms on the carbon skeleton of the piperidin-1-yl or hexahydroazepin-1-yl group are replaced by a straight-chain alkylene bridge, this bridge containing 2 to 5 carbon atoms if the two hydrogen atoms are on the same carbon atom, or 1 to 4 carbon atoms if the hydrogen atoms are on adjacent carbon atoms, or 1 to 4 carbon atoms if the hydrogen atoms are on carbon atoms which are separated by one atom, or 1 to 3 carbon atoms if the hydrogen atoms are on carbon atoms which are separated by two atoms,

an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl or hexahydroazepin-1-yl group which is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a piperazin-1-yl or [1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two C_{1-3}-alkyl groups,

a 3-imino-piperazin-1-yl, 3-imino-[1,4]diazepan-1-yl or 5-imino-[1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two C_{1-3}-alkyl groups,

a [1,4]diazepan-1-yl group optionally substituted by one or two C_{1-3}-alkyl groups which is substituted in the 6 position by an amino group,

a C_{3-7}-cycloalkyl group which is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkyl group which is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a C_{3-7}-cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, while the two nitrogen atoms on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

an N-(C_{3-7}-cycloalkyl)-N-(C_{1-3}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, while the two nitrogen atoms on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

a C_{3-7}-cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

an N-(C_{3-7}-cycloalkyl)-N-(C_{1-3}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an N-(C_{3-7}-cycloalkyl-C_{1-2}-alkyl)-N-(C_{1-2}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

an N-(C_{3-7}-cycloalkyl-C_{1-2}-alkyl)-N-(C_{1-2}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

an R^{19}-C_{2-4}-alkylamino group wherein R^{19} is separated from the nitrogen atom of the C_{2-4}-alkylamino moiety by at least two carbon atoms and

R^{19} denotes an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an R^{19}-C_{2-4}-alkylamino group wherein the nitrogen atom of the C_{2-4}-alkylamino moiety is substituted by a C_{1-3}-alkyl group and R^{19} is separated from the nitrogen atom of the C_{2-4}-alkylamino moiety by at least two carbon atoms, where R^{19} is as hereinbefore defined,

an amino group substituted by the group R^{20} wherein

R^{20} denotes an azetidin-3-yl, azetidin-2-ylmethyl, azetidin-3-ylmethyl, pyrrolidin-3-yl, pyrrolidin-2-ylmethyl, pyrrolidin-3-ylmethyl, piperidin-3-yl, piperidin-4-yl, piperidin-2-ylmethyl, piperidin-3-ylmethyl or piperidin-4-

ylmethyl group, while the groups mentioned for R^{20} may each be substituted by one or two C_{1-3}-alkyl groups,

an amino group substituted by the group R^{20} and a C_{1-3}-alkyl group wherein R^{20} is as hereinbefore defined, while the groups mentioned for R^{20} may each be substituted by one or two C_{1-3}-alkyl groups,

an R^{19}-C_{3-4}-alkyl group wherein the C_{3-4}-alkyl moiety is straight-chained and may additionally be substituted by one or two C_{1-3}-alkyl groups, where R^{19} is as hereinbefore defined,

a 3-amino-2-oxo-piperidin-5-yl or 3-amino-2-oxo-1-methyl-piperidin-5-yl group,

a pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, hexahydroazepin-3-yl or hexahydroazepin-4-yl group which is substituted in the 1 position by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)amino group,

or an azetidin-2-yl-C_{1-2}-alkyl, azetidin-3-yl-C_{1-2}-alkyl, pyrrolidin-2-yl-C_{1-2}-alkyl, pyrrolidin-3-yl, pyrrolidin-3-yl-C_{1-2}-alkyl, piperidin-2-yl-C_{1-2}-alkyl, piperidin-3-yl, piperidin-3-yl-C_{1-2}-alkyl, piperidin-4-yl or piperidin-4-yl-C_{1-2}-alkyl group, while the above mentioned groups may each be substituted by one or two C_{1-3}-alkyl groups,

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, which may be mono- or disubstituted by R_h independently of one another, where the substituents are identical or different and R_h denotes a fluorine, chlorine, bromine or iodine atom, a trifluoromethyl, cyano, nitro, amino, aminocarbonyl, aminosulphonyl, methylsulphonyl, acetylamino, methylsulphonylamino, C_{1-3}-alkyl, cyclopropyl, ethenyl, ethynyl, hydroxy, C_{1-3}-alkyloxy, difluoromethoxy or trifluoromethoxy group,

by the heteroaryl groups mentioned in the definitions of the above mentioned groups are meant a pyrrolyl, furanyl, thienyl, pyridyl, indolyl, benzofuranyl, benzothiophenyl, quinolinyl or isoquinolinyl group,

or a pyrrolyl, furanyl, thienyl or pyridyl group wherein one or two methyne groups are replaced by nitrogen atoms,

or an indolyl, benzofuranyl, benzothiophenyl, quinolinyl or isoquinolinyl group wherein one to three methyne groups are replaced by nitrogen atoms,

or a 1,2-dihydro-2-oxo-pyridinyl, 1,4-dihydro-4-oxo-pyridinyl, 2,3-dihydro-3-oxo-pyridazinyl, 1,2,3,6-tetrahydro-3,6-dioxo-pyridazinyl, 1,2-dihydro-2-oxo-pyrimidinyl, 3,4-dihydro-4-oxo-pyrimidinyl, 1,2,3,4-tetrahydro-2,4-dioxo-pyrimidinyl, 1,2-dihydro-2-oxo-pyrazinyl, 1,2,3,4-tetrahydro-2,3-dioxo-pyrazinyl, 2,3-dihydro-2-oxo-indolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-oxo-1*H*-benzimidazolyl, 2,3-dihydro-2-oxo-benzoxazolyl, 1,2-dihydro-2-oxo-quinolinyl, 1,4-dihydro-4-oxo-quinolinyl, 1,2-dihydro-1-oxo-isoquinolinyl, 1,4-dihydro-4-oxo-cinnolinyl, 1,2-dihydro-2-oxo-quinazolinyl, 3,4-dihydro-4-oxo-quinazolinyl, 1,2,3,4-tetrahydro-2,4-dioxo-quinazolinyl, 1,2-dihydro-2-oxoquinoxalinyl, 1,2,3,4-tetrahydro-2,3-dioxo-quinoxalinyl, 1,2-dihydro-1-oxo-phthalazinyl, 1,2,3,4-tetrahydro-1,4-dioxo-phthalazinyl, chromanyl, cumarinyl, 2,3-dihydro-benzo[1,4]dioxinyl or 3,4-dihydro-3-oxo-2*H*-benzo[1,4]oxazinyl group,

and the above mentioned heteroaryl groups may be mono- or disubstituted by R_h, while the substituents may be identical or different and R_h is as hereinbefore defined,

and, unless otherwise stated, the above mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof, the prodrugs thereof and the salts thereof.

Compounds which contain a group that can be cleaved *in vivo* are prodrugs of the corresponding compounds in which this group that can be cleaved *in vivo* has been cleaved.

The carboxy groups mentioned in the definition of the above mentioned groups may be replaced by a group which can be converted into a carboxy group *in vivo* or by a group which is negatively charged under physiological conditions,

and furthermore the amino and imino groups mentioned in the definition of the above mentioned groups may be substituted by a group which can be cleaved *in vivo*. Such groups are described for example in WO 98/46576 and by N.M. Nielsen *et al.* in International Journal of Pharmaceutics 39, 75-85 (1987).

By a group which can be converted *in vivo* into a carboxy group is meant, for example, a hydroxymethyl group, a carboxy group esterified with an alcohol wherein the alcohol moiety is preferably a C_{1-6}-alkanol, a phenyl-C_{1-3}-alkanol, a C_{3-9}-cycloalkanol, while a C_{5-8}-cycloalkanol may additionally be substituted by one or two C_{1-3}-alkyl groups, a C_{5-8}-cycloalkanol wherein a methylene group in the 3 or 4 position is replaced by an oxygen atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl, phenyl-C_{1-3}-alkyloxycarbonyl or C_{2-6}-alkanoyl group and the cycloalkanol moiety may additionally be substituted by one or two C_{1-3}-alkyl groups, a C_{4-7}-cycloalkenol, a C_{3-5}-alkenol, a phenyl-C_{3-5}-alkenol, a C_{3-5}-alkynol or phenyl-C_{3-5}-alkynol with the proviso that no bonds to the oxygen atom start from a carbon atom which carries a double or triple bond, a C_{3-8}-cycloalkyl-C_{1-3}-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms which may additionally be substituted in the bicycloalkyl moiety by one or two C_{1-3}-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula

$$R_p\text{-}CO\text{-}O\text{-}(R_qCR_r)\text{-}OH,$$

wherein

R_p denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, C_{1-8}-alkyloxy, C_{5-7}-cycloalkyloxy, phenyl or phenyl-C_{1-3}-alkyl group,

R_q denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_r denotes a hydrogen atom or a C_{1-3}-alkyl group,

by a group which is negatively charged under physiological conditions is meant, for example, a tetrazol-5-yl, phenylcarbonylaminocarbonyl, trifluoromethylcarbonylaminocarbonyl, C_{1-6}-alkylsulphonylamino, phenylsulphonylamino, benzylsulphonylamino, trifluoromethylsulphonylamino, C_{1-6}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, benzylsulphonylaminocarbonyl or perfluoro-C_{1-6}-alkylsulphonylaminocarbonyl group

and by a group which can be cleaved *in vivo* from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as a phenylcarbonyl group optionally mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-3}-alkyl or C_{1-3}-alkyloxy groups, while the substituents may be identical or different, a pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, a 3,3,3-trichloropropionyl or allyloxycarbonyl group, a C_{1-16}-alkyloxycarbonyl or C_{1-16}-alkylcarbonyloxy group, wherein hydrogen atoms may be wholly or partially replaced by fluorine or chlorine atoms such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, hexadecyloxycarbonyl, methylcarbonyloxy, ethylcarbonyloxy, 2,2,2-trichloroethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy, butylcarbonyloxy, tert.butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, octylcarbonyloxy, nonylcarbonyloxy, decylcarbonyloxy, undecylcarbonyloxy, dodecylcarbonyloxy or hexadecylcarbonyloxy group, a phenyl-C_{1-6}-alkyloxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a 3-amino-propionyl group wherein the amino group may be mono- or disubstituted by C_{1-6}-alkyl or C_{3-7}-cycloalkyl groups and the substituents may

be identical or different, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkyloxycarbonyl, C_{1-3}-alkyloxy-C_{2-4}-alkyloxy-C_{2-4}-alkyloxycarbonyl, R_p-CO-O-(R_qCR_r)-O-CO, C_{1-6}-alkyl-CO-NH-(R_sCR_t)-O-CO- or C_{1-6}-alkyl-CO-O-(R_sCR_t)-(R_sCR_t)-O-CO- group, wherein R_p to R_r are as hereinbefore defined,

R_s and R_t, which may be identical or different, denote hydrogen atoms or C_{1-3}-alkyl groups.

Moreover, the saturated alkyl and alkyloxy moieties which contain more than 2 carbon atoms mentioned in the foregoing definitions and those that follow, unless otherwise stated, also include the branched isomers thereof such as, for example, the isopropyl, tert.butyl, isobutyl group, etc.

Preferred compounds of general formula I are those wherein

R^1, R^2 and R^3 are as hereinbefore defined and

R^4 denotes a pyrrolidin-1-yl group which is substituted in the 3 position by an amino group,

a piperidin-1-yl group which is substituted in the 3 position by an amino group,

a hexahydroazepin-1-yl group which is substituted in the 3 position or 4 position by an amino group,

a (2-aminocyclohexyl)amino group,

a cyclohexyl group which is substituted in the 3 position by an amino group, or

an N-(2-aminoethyl)-methylamino or an N-(2-aminoethyl)-ethylamino group,

while, unless otherwise stated, the above mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and salts thereof.

Particularly preferred compounds of general formula I are those wherein

R^1 denotes a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by R^{10}, while

R^{10} denotes a formylamino group,

a C_{3-7}-cycloalkyl-carbonylamino or C_{3-7}-cycloalkyl-C_{1-3}-alkyl-carbonylamino group,

a C_{6-9}-bicycloalkyl-carbonylamino group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein

a methylene group is replaced by an oxygen or sulphur atom or by an imino, sulphinyl or sulphonyl group,

a (1,3-dioxolanyl)-carbonylamino, (1,4-dioxanyl)-carbonylamino, morpholin-2-yl-carbonylamino, morpholin-3-ylcarbonylamino or piperazin-2-yl-carbonylamino group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2$ group is replaced by an –NH-CO group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2-CH_2$ group is replaced by an –NH-CO-O group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a methylene group is replaced by a carbonyl group,

a C_{5-7}-cycloalkenyl-carbonylamino or C_{5-7}-cycloalkenyl-C_{1-3}-alkyl-carbonylamino group,

a C_{3-7}-cycloalkyl-sulphonylamino, phenylsulphonylamino or phenyl-C_{1-3}-alkyl-sulphonylamino group or

a pyridinylcarbonylamino group,

R^2 denotes a hydrogen atom,

or a C_{1-3}-alkyl group,

R^3 denotes a C_{4-6}-alkenyl group,

a 2-butyn-1-yl group or

a 1-cyclopenten-1-yl-methyl group

and

R^4 denotes a piperidin-1-yl group which is substituted in the 3 position by an amino group,

a hexahydroazepin-1-yl group which is substituted in the 3 position or 4 position by an amino group,

a (2-aminocyclohexyl)amino group,

a cyclohexyl group which is substituted in the 3 position by an amino group, or

an N-(2-aminoethyl)-methylamino or an N-(2-aminoethyl)-ethylamino group,

while, unless otherwise stated, the above mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

Most particularly preferred compounds of general formula I are those wherein

R^1 denotes a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by a formylamino, pyridinylcarbonylamino or cyclopropylcarbonylamino group,

R^2 denotes a methyl group,

R^3 denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group or

a 2-butyn-1-yl group

and

R^4 denotes a (3-amino-piperidin-1-yl) group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof,

but particularly those compounds of general formula I wherein

R^1 denotes a [2-(cyclopropylcarbonylamino)-phenyl]-carbonylmethyl or [2-(pyridylcarbonylamino)-phenyl]-carbonylmethyl group,

R^2 denotes a methyl group,

R^3 denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group or

a 2-butyn-1-yl group

and

R^4 denotes a (3-amino-piperidin-1-yl) group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

The following compounds of general formula I are particularly preferred:

(1) 1-[2-(2-formylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

(2) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

(3) 1-[2-(2-formylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

(4) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-((E)-2-buten-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,

(5) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-((E)-2-buten-1-yl)-8-((*S*)-3-amino-piperidin-1-yl)-xanthine,

(6) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,

(7) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-((*S*)-3-amino-piperidin-1-yl)-xanthine and

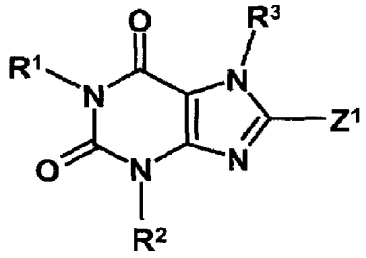
(8) 1-[2-(2-{[(pyridin-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

as well as the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

According to the invention the compounds of general formula I are obtained by methods known *per se*, for example by the following methods:

a) In order to prepare compounds of general formula I wherein R^4 is one of the above mentioned groups linked to the xanthine skeleton via a nitrogen atom:

reacting a compound of general formula



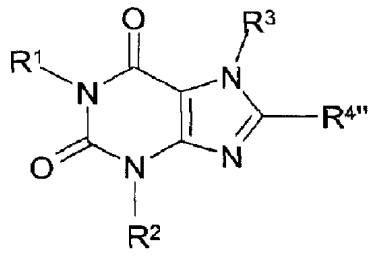
(II),

wherein
R^1 to R^3 are as hereinbefore defined and
Z^1 denotes a leaving group such as a halogen atom, a substituted hydroxy, mercapto, sulphinyl, sulphonyl or sulphonyloxy group, such as for example a chlorine or bromine atom, a methanesulphonyl or methanesulphonyloxy group,
with an amine of general formula $R^{4'}$-H, wherein $R^{4'}$ denotes one of the groups mentioned hereinbefore for R^4 which is linked to the xanthine skeleton via a nitrogen atom.

The reaction is expediently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulphoxide, ethyleneglycol monomethylether, ethyleneglycol diethylether or sulpholane, optionally in the presence of an inorganic or tertiary organic base, e.g. sodium carbonate, potassium carbonate or potassium hydroxide, a tertiary organic

base, e.g. triethylamine, or in the presence of N-ethyl-diisopropylamine (Hünig base), while these organic bases may simultaneously also serve as solvent, and optionally in the presence of a reaction accelerator such as an alkali metal halide or a palladium-based catalyst at temperatures between -20 and 180°C, but preferably at temperatures between -10 and 120°C. The reaction may however also be carried out without a solvent or in an excess of the amine of general formula $R^{4'}$-H.

b) deprotecting a compound of general formula



(III),

wherein R^1, R^2 and R^3 are as hereinbefore defined and
$R^{4''}$ denotes one of the groups mentioned for R^4 hereinbefore which contain an imino, amino or alkylamino group, while the imino, amino or alkylamino group is substituted by a protective group, optionally followed by subsequent alkylation of the imino, amino or C_{1-3}-alkylamino group.

The liberating of an amino group from a protected precursor is a standard reaction in synthetic organic chemistry. There are many examples of suitable protective groups. A summary of the chemistry of protective groups can be found in Theodora W.Greene and Peter G.M.Wuts, Protective Groups in Organic Synthesis, Second Edition, 1991, published by John Wiley and Sons, and in Philip J. Kocienski, Protecting Groups, published by Georg Thieme, 1994.

The following are examples of protective groups:

the tert.-butyloxycarbonyl group which can be cleaved by treating with an acid such as for example trifluoroacetic acid or hydrochloric acid or by treating with bromotrimethylsilane or iodotrimethylsilane, optionally using a solvent such as methylene chloride, ethyl acetate, dioxane, methanol, isopropanol or diethylether at temperatures between 0°C and 80°C,

the 2,2,2-trichloroethoxycarbonyl group which can be cleaved by treating with metals such as for example zinc or cadmium in a solvent such as acetic acid or a mixture of tetrahydrofuran and a weak aqueous acid at temperatures between 0°C and the boiling temperature of the solvent used and

the carbobenzyloxycarbonyl group which can be cleaved for example by hydrogenolysis in the presence of a noble metal catalyst such as for example palladium-charcoal and a solvent such as for example alcohols, ethyl acetate, dioxane, tetrahydrofuran or mixtures of these solvents at temperatures between 0°C and the boiling point of the solvent, by treating with boron tribromide in methylene chloride at temperatures between –20°C and ambient temperature, or by treating with aluminium chloride/anisol at temperatures between 0°C and ambient temperature.

The optional subsequent introduction of a C_{1-3}-alkyl group may be done by alkylation or reductive alkylation.

The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethyl sulphate, optionally in the presence of a tertiary organic base or in the presence of an inorganic base, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The subsequent reductive alkylation is carried out with a corresponding carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde or

acetone in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride, conveniently at a pH of 6-7 and at ambient temperature or in the presence of a hydrogenation catalyst, e.g. with hydrogen in the presence of palladium/charcoal, under a hydrogen pressure of 1 to 5 bar. The methylation may also be carried out in the presence of formic acid as reducing agent at elevated temperatures, e.g. at temperatures between 60 and 120°C.

In the reactions described hereinbefore, any reactive groups present such as carboxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a carboxy group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group,

protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such

as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisol.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxan, methanol or diethylether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C, or by treating with sodium hydroxide solution, optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxan at temperatures between 20 and 50°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using

methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms racemic salts or derivatives such as e.g. esters or amides of an optically active substance, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II and III used as starting materials are either known from the literature in some cases or may be obtained by methods known from the literature (cf. Examples I to VII).

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on the enzyme DPP-IV.

The biological properties of the new compounds were investigated as follows:

The ability of the substances and their corresponding salts to inhibit the DPP-IV activity can be demonstrated in a test set-up in which an extract of human colon carcinoma cell line Caco-2 is used as the DPP IV source. The differentiation of the cells in order to induce the DPP-IV expression was carried out as described by Reiher et al. in an article entitled "Increased expression of intestinal cell line Caco-2" , which appeared in Proc. Natl. Acad. Sci. Vol. 90, pages 5757-5761 (1993). The cell extract was obtained from cells solubilised in a buffer (10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5% Nonidet-P40, pH 8.0) by centrifuging at 35,000 g for 30 minutes at 4°C (to remove cell debris).

The DPP-IV assay was carried out as follows:

50 µl substrate solution (AFC; AFC is amido-4-trifluoromethylcoumarin), final concentration 100 µM, were placed in black microtitre plates. 20 µl of assay buffer (final concentrations 50 mM Tris HCl pH 7.8, 50 mM NaCl, 1 % DMSO) was pipetted in. The reaction was started by adding 30 µl of solubilised Caco-2 protein (final concentration 0.14 µg of protein per well). The test substances to be investigated were typically added prediluted in 20 µl, and the volume of assay buffer was then reduced accordingly. The reaction was carried out at ambient temperature, incubating for 60 minutes. Then the fluorescence was measured in a Victor 1420 Multilabel Counter, the excitation wavelength being 405 nm and the emission wavelength being 535 nm. Blank readings

(corresponding to 0 % activity) were obtained in mixtures without any Caco-2 protein (volume replaced by assay buffer), control values (corresponding to 100 % activity) were obtained in mixtures with no substance added. The potency of the test substances in question, expressed as IC_{50} values, was calculated from dosage/activity curves consisting of 11 measuring points in each case. The following results were obtained:

Compound (Example No.)	DPP IV inhibition IC_{50} [nM]
1	5
1(1)	11
1(2)	3
1(3)	4
1(4)	3
1(5)	3
1(6)	5
1(7)	8

The compounds prepared according to the invention are well tolerated, as for example when 10 mg/kg of the compound of Example 1(5) were administered to rats by oral route no changes in the animals' behaviour could be detected.

In view of their ability to inhibit DPP-IV activity, the compounds of general formula I according to the invention and the corresponding pharmaceutically acceptable salts thereof are suitable for treating all those conditions or illnesses which can be influenced by the inhibition of the DPP-IV activity. It is therefore to be expected that the compounds according to the invention will be suitable for the prevention or treatment of diseases or conditions such as type 1 and type 2 diabetes mellitus, diabetic complications (such as e.g. retinopathy, nephropathy or neuropathies), metabolic acidosis or ketosis, reactive hypoglycaemia, insulin resistance, metabolic syndrome, dyslipidaemias of various origins, arthritis, atherosclerosis and related diseases, obesity, allograft transplantation and calcitonin-induced

osteoporosis. In addition these substances are capable of preventing B-cell degeneration such as e.g. apoptosis or necrosis of pancreatic B-cells. The substances are also suitable for improving or restoring the function of pancreatic cells and also increasing the number and size of pancreatic B-cells. Additionally, and on the basis of the role of the Glucagon-Like Peptides, such as e.g. GLP-1 and GLP-2 and their link with DPP-IV inhibition, it is likely that the compounds according to the invention are suitable for achieving, inter alia, a sedative or anxiety-relieving effect and also of favourably affecting catabolic states after operations or hormonal stress responses or of reducing mortality or morbidity after myocardial infarct. They are also suitable for treating all conditions which are connected with the above mentioned effects and which are mediated by GLP-1 or GLP-2. The compounds according to the invention may also be used as diuretics or antihypertensives and are suitable for preventing and treating acute renal failure. Furthermore, the compounds according to the invention may be used to treat inflammatory diseases of the respiratory tract. They are also suitable for the prevention and treatment of chronic inflammatory intestinal diseases such as e.g. irritable bowel syndrome (IBS), Crohn's disease or ulcerative colitis and also pancreatitis. It is also likely that they can be used for all kinds of damage to or impairment of the gastrointestinal tract such as colitis and enteritis, for example. It is also expected that DPP-IV inhibitors and hence also the compounds according to the invention may be used to treat infertility or to improve fertility in humans or mammals, particularly when the infertility is connected with insulin resistance or polycystic ovary syndrome. On the other hand these substances are suitable for affecting sperm motility and can thus be used as male contraceptives. The substances are also suitable for treating deficiencies of growth hormone which are associated with reduced stature, and may also be used to advantage in any indications in which growth hormone may be used. The compounds according to the invention are also suitable, on the basis of their inhibitory effect on DPP IV, for treating various autoimmune diseases such as e.g. rheumatoid arthritis, multiple sclerosis, thyroiditis and Basedow's disease, etc. They may also be used to treat viral diseases and also, for example, in HIV infections, for stimulating blood production, in benign prostatic hyperplasia, gingivitis, as well as for the treatment of neuronal

defects and neurodegenerative diseases such as Alzheimer's disease, for example. The compounds described may also be used for the treatment of tumours, particularly for modifying tumour invasion and also metastasisation; examples here are their use in treating T-cell lymphomas, acute lymphoblastic leukaemia, cell-based pancreatic carcinomas, basal cell carcinomas or breast cancers. Other indications are stroke, ischaemia of various origins, Parkinson's disease and migraine. In addition, further indications include follicular and epidermal hyperkeratoses, increased keratinocyte proliferation, psoriasis, encephalomyelitis, glomerulonephritis, lipodystrophies, as well as psychosomatic, depressive and neuropsychiatric diseases of all kinds.

The compounds according to the invention may also be used in conjunction with other active substances. Therapeutic agents which are suitable for such combinations include, for example, antidiabetics, such as metformin, sulphonylureas (e.g. glibenclamid, tolbutamid, glimepiride), nateglinide, repaglinide, thiazolidinedione (e.g. rosiglitazone, pioglitazone), PPAR-gamma agonists (e.g. GI 262570) and antagonists, PPAR-gamma/alpha modulators (e.g. KRP 297), alpha-glucosidase inhibitors (e.g. acarbose, voglibose), other DPPIV inhibitors, alpha2 antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g. exendin-4) or amylin. Also, SGLT2 inhibitors such as T-1095, inhibitors of protein tyrosine phosphatase 1, substances which influence deregulated glucose production in the liver, such as e.g. inhibitors of glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen - phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol - pyruvate carboxykinase, glycogen synthase kinase or pyruvate dehydrokinase, lipid lowering agents, such as HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate, fenofibrate), nicotinic acid and its derivatives, PPAR-alpha agonists, PPAR-delta agonists, ACAT inhibitors (e.g. avasimibe) or cholesterol resorption inhibitors such as for example ezetimibe, bile acid-binding substances such as for example cholestyramine, inhibitors of ileac bile acid transport, HDL-raising compounds such as for example inhibitors of CETP or regulators of ABC1 or active substances for the treatment of obesity, such as e.g. sibutramine or tetrahydrolipostatin, dexfenfluramine, axokine, antagonists of the

cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists or $ß_3$-agonists such as SB-418790 or AD-9677 as well as agonists of the 5HT2c receptor.

It is also possible to combine the compounds with drugs for treating high blood pressure such as e.g. All antagonists or ACE inhibitors, diuretics, ß-blockers, Ca-antagonists, etc., or combinations thereof.

The dosage required to achieve such an effect is expediently, by intravenous route, 1 to 100 mg, preferably 1 to 30 mg, and by oral route 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 a day. For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples that follow are intended to illustrate the invention:

Preparation of the starting compounds:

Example I

1-[2-(2-formylamino-phenyl)-2-oxo-ethyl]- 3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

A mixture of 1.2 ml of formic acid and 2 ml of acetic acid anhydride is heated to 60°C for 10 minutes. Then 1 ml of this mixture is added to 226 mg of 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine and the reaction mixture is stirred for 15 minutes at 80°C. For working up, the reaction mixture is combined with methylene chloride and slowly made alkaline with saturated potassium carbonate solution. The aqueous phase is extracted with methylene chloride and the combined organic phases are dried over sodium sulphate and evaporated down. The crude product is further reacted without any more purification.

Yield: 186 mg (78 % of theory)

R_f value: 0.40 (silica gel, cyclohexane/ethyl acetate = 3:7)

Mass spectrum (ESI^+): m/z = 594 $[M+H]^+$

The following compounds are obtained analogously to Example I:

(1) 1-[2-(2-formylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.23 (silica gel, cyclohexane/ethyl acetate = 3:7)

Mass spectrum (ESI^+): m/z = 578 $[M+H]^+$

Example II

1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

Prepared by treating von 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-

xanthine with powdered iron in a mixture of ethanol, water and glacial acetic acid (150:50:14) at 90°C.
Mass spectrum (ESI$^+$): m/z = 566 $[M+H]^+$

The following compounds are obtained analogously to Example II:

(1) 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine
Mass spectrum (ESI$^+$): m/z = 430, 432 $[M+H]^+$

(2) 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
Mass spectrum (ESI$^+$): m/z = 552 $[M+H]^+$

(3) 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-bromo-xanthine
R_f value: 0.62 (silica gel, cyclohexane/ethyl acetate = 4:6)
Mass spectrum (ESI$^+$): m/z = 432, 434 $[M+H]^+$

Example III

1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

2.20 g of 3-tert.-butyloxycarbonylamino-piperidine are added at 65°C to 4.40 g of 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-chloro-xanthine and 1.30 g of sodium carbonate in 50 ml of dimethylsulphoxide. The reaction mixture is stirred for approx. 16 h at 65°C. After cooling to ambient temperature it is poured onto a mixture of 600 ml of water and 100 g of ice. The precipitate formed is suction filtered and washed with water. The filter cake is dissolved in diethyl ether, the solution is dried and evaporated down. The brown resinous flask residue is brought to crystallisation with diisopropylether.
Yield: 3.30 g (54 % of theory)

R_f value: 0.52 (silica gel, cyclohexane/ethyl acetate = 3:7)
Mass spectrum (ESI^+): m/z = 596 $[M+H]^+$

The following compounds are obtained analogously to Example III:

(1) 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.50 (silica gel, methylene chloride/methanol = 95:5)
Mass spectrum (ESI^+): m/z = 550 $[M+H]^+$

(2) 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.50 (silica gel, cyclohexane/ethyl acetate = 1:2)

(3) 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[(*S*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.40 (silica gel, cyclohexane/ethyl acetate = 4:6)
Mass spectrum (ESI^+): m/z = 552 $[M+H]^+$

(4) 3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
Melting point: 197-200°C
Mass spectrum (ESI^+): m/z = 417 $[M+H]^+$

(5) 3-methyl-7-(2-butyn-1-yl)-8-[(*S*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.52 (silica gel, ethyl acetate)
Mass spectrum (ESI^+): m/z = 417 $[M+H]^+$

(6) 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.20 (silica gel, cyclohexane/ethyl acetate = 1:1)
Mass spectrum (ESI^+): m/z = 552 $[M+H]^+$

Example IV

1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-chloro-xanthine

A mixture of 6.02 g of 3-methyl-7-(3-methyl-2-buten-1-yl)-8-chloro-xanthine, 5.86 g of 2-bromo-1-(2-nitro-phenyl)-ethanone and 5.00 g of potassium carbonate in 150 ml of N,N-dimethylformamide is stirred for approx. 26 h at 60°C. For working up the cooled reaction mixture is poured onto a mixture of 500 ml of 1 N sodium hydroxide solution and 200 g of ice. The precipitate formed is suction filtered and dried.

Yield: 6.32 g (65 % of theory)

R_f value: 0.50 (silica gel, cyclohexane/ethyl acetate = 4:6)

Mass spectrum (ESI^+): m/z = 432, 434 $[M+H]^+$

The following compounds are obtained analogously to Example IV:

(1) 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine

R_f value: 0.77 (silica gel, methylene chloride/methanol = 95:5)

Mass spectrum (ESI^+): m/z = 460, 462 $[M+H]^+$

(2) 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-bromo-xanthine

R_f value: 0.50 (silica gel, cyclohexane/ethyl acetate = 1:1)

Mass spectrum (ESI^+): m/z = 462, 464 $[M+H]^+$

(3) 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.60 (silica gel, methylene chloride/methanol = 95:5)

(4) 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*S*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.60 (silica gel, methylene chloride/methanol = 95:5)

Mass spectrum (ESI$^+$): m/z = 580 $[M+H]^+$

Example V

3-methyl-7-(3-methyl-2-buten-1-yl)-8-chloro-xanthine

5.87 ml of 1-bromo-3-methyl-2-butene are added to 10.56 g of 3-methyl-8-chloro-xanthine and 17 ml of Hünig base in 100 ml of N,N-dimethylformamide. The reaction mixture is stirred for approx. 10 minutes at ambient temperature and then combined with 800 ml of water. The light-coloured precipitate formed is suction filtered, washed with ethanol and diethyl ether and dried.
Yield: 10.56 g (81 % of theory)
Mass spectrum (ESI$^+$): m/z = 269, 271 $[M+H]^+$

The following compounds are obtained analogously to Example V:

(1) 3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine
R_f value: 0.72 (silica gel, ethyl acetate)
Mass spectrum (ESI$^+$): m/z = 297, 299 $[M+H]^+$

(2) 3-methyl-7-((E)-2-buten-1-yl)-8-bromo-xanthine
Mass spectrum (ESI$^+$): m/z = 299, 301 $[M+H]^+$

Example VI

1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

A mixture of 242 mg of 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine and 44 µl of pyridine in N,N-dimethylformamide is combined with 39 µl of cyclopropanecarboxylic acid chloride and stirred for 2 h at 80°C. Then another 20 µl of pyridine and 30 µl of cyclopropanecarboxylic acid chloride are

added. After a further 10 h at 80°C the cooled reaction mixture is diluted with methylene chloride and combined with water. The aqueous phase is extracted with methylene chloride and the combined organic phases are evaporated down. The crude product is purified through a silica gel column with cyclohexane/ethyl acetate (7:3 to 4:6) as eluant.
Yield: 90 mg (33 % of theory)
R_f value: 0.60 (silica gel, cyclohexane/ethyl acetate = 3:7)

The following compounds are obtained analogously to Example VI:

(1) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.30 (silica gel, cyclohexane/ethyl acetate/isopropanol = 8:1:1)
Mass spectrum (ESI^+): m/z = 620 $[M+H]^+$

(2) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-((E)-2-buten-1-yl)-8-[(*S*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.53 (silica gel, cyclohexane/ethyl acetate/isopropanol = 14:3:3)
Mass spectrum (ESI^+): m/z = 620 $[M+H]^+$

(3) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.35 (silica gel, methylene chloride/methanol = 95:5)
Mass spectrum (ESI^+): m/z = 618 $[M+H]^+$

(4) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-[(*S*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.35 (silica gel, methylene chloride/methanol = 95:5)
Mass spectrum (ESI^+): m/z = 618 $[M+H]^+$

(5) 1-[2-(2-{[(pyridin-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.55 (silica gel, cyclohexane/ethyl acetate/isopropanol = 14:3:3)
Mass spectrum (ESI^+): m/z = 657 $[M+H]^+$

Example VII

1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

Prepared by reduction of 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine with sodium dithionite in a mixture of methylglycol and water (3:2) at 100°C.
R_f value: 0.50 (silica gel, cyclohexane/ethyl acetate = 4:6)

The following compounds are obtained analogously to Example VII:

(1) 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*S*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.34 (silica gel, methylene chloride/methanol = 95:5)

Preparation of the final compounds:

Example 1

1-[2-(2-formylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

A solution of 180 mg of 1-[2-(2-formylamino-phenyl)-2-oxo-ethyl]- 3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine in 4 ml of methylene chloride is combined with 1 ml of trifluoroacetic acid and stirred for half an hour at ambient temperature. For working up the reaction mixture is made slightly alkaline with 1 N sodium hydroxide solution and the aqueous phase is extracted with methylene chloride. The combined organic phases are evaporated down and purified through a silica gel column.
Yield: 130 mg (87 % of theory)

R_f value: 0.38 (Ready-made reversed phase TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 100:100:0.1)
Mass spectrum (ESI^+): m/z = 494 $[M+H]^+$

The following compounds are obtained analogously to Example 1:

(1) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
R_f value: 0.35 (Ready-made reversed phase TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 100:100:0.1)
Mass spectrum (ESI^+): m/z = 534 $[M+H]^+$

(2) 1-[2-(2-formylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
R_f value: 0.20 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)
Mass spectrum (ESI^+): m/z = 478 $[M+H]^+$

(3) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-((E)-2-buten-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine
R_f value: 0.50 (Ready-made reversed phase TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:0.1)
Mass spectrum (ESI^+): m/z = 520 $[M+H]^+$

(4) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-((E)-2-buten-1-yl)-8-((*S*)-3-amino-piperidin-1-yl)-xanthine
R_f value: 0.50 (Ready-made reversed phase TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:0.1)
Mass spectrum (ESI^+): m/z = 520 $[M+H]^+$

(5) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 518 $[M+H]^+$

(6) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-((*S*)-3-amino-piperidin-1-yl)-xanthine
R_f value: 0.14 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)
Mass spectrum (ESI^+): m/z = 518 $[M+H]^+$

(7) 1-[2-(2-{[(pyridin-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 557 $[M+H]^+$

The following compounds may also be obtained analogously to the foregoing Examples and other methods known from the literature:

(1) 1-(2-{2-[(cyclobutylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(2) 1-(2-{2-[(cyclopentylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(3) 1-(2-{2-[(cyclohexylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-((E)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(4) 1-(2-{2-[(cycloheptylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(5) 1-[2-(2-{[(bicyclo[2.2.1]heptan-1-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(6) 1-[2-(2-{[(bicyclo[2.2.2]octan-1-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(7) 1-[2-(2-{[(1-cyclobuten-1-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(8) 1-[2-(2-{[(1-cyclopenten-1-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine

(9) 1-[2-(2-{[(1-cyclohexen-1-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(10) 1-[2-(2-{[(2-oxo-cyclohexane-1-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine

(11) 1-[2-(2-{[(2,6-dioxo-cyclohexane-1-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine

(12) 1-[2-(2-{[(tetrahydro-furan-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(13) 1-[2-(2-{[(tetrahydro-furan-3-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(14) 1-[2-(2-{[(tetrahydro-thiophen-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine

(15) 1-[2-(2-{[(tetrahydro-thiophen-3-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(16) 1-[2-(2-{[(1-oxo-tetrahydro-thiophen-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine

(17) 1-[2-(2-{[(1,1-dioxo-tetrahydro-thiophen-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine

(18) 1-[2-(2-{[(pyrrolidin-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(19) 1-[2-(2-{[(pyrrolidin-3-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(20) 1-[2-(2-{[(tetrahydro-pyran-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(21) 1-[2-(2-{[([1,3]dioxolan-4-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-1-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(22) 1-[2-(2-{[([1,4]dioxane-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(23) 1-[2-(2-{[(morpholin-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(24) 1-[2-(2-{[(piperazin-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(25) 1-[2-(2-{[(5-oxo-pyrrolidin-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine

(26) 1-[2-(2-{[(6-oxo-piperidin-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(27) 1-[2-(2-{[(2-oxo-oxazolidin-4-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-1-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(28) 1-[2-(2-{[(cyclopropylmethyl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(29) 1-[2-(2-{[(pyridin-3-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(30) 1-(2-{2-[(cyclopropylsulphonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(31) 1-(2-{2-[(phenylsulphonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(32) 1-(2-{2-[(benzylsulphonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

Example 2

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	1.5 mg
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg

die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

Example 3

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

Example 4

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

die: 10 mm, flat

Example 5

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance		150.0 mg
corn starch (dried)	approx.	80.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		3.0 mg
	approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

Example 6

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 7

Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavouring	0.30 g
dist. water ad	100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 8

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example 9

Ampoules containing 50 mg of active substance

Composition:

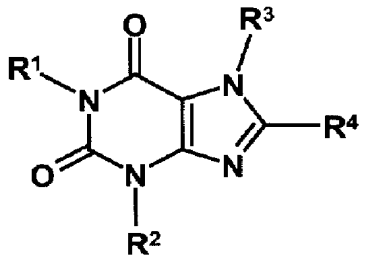
active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Patent Claims

1. Compounds of general formula



(I),

wherein

R^1 denotes a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by R^{10} and R^{11}, where

R^{10} denotes a formylamino group,

a C_{3-7}-cycloalkyl-carbonylamino or C_{3-7}-cycloalkyl-C_{1-3}-alkyl-carbonyl-amino group,

a C_{6-9}-bicycloalkyl-carbonylamino or C_{6-9}-bicycloalkyl-C_{1-3}-alkyl-carbonylamino group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein

a methylene group is replaced by an oxygen or sulphur atom or by an imino, sulphinyl or sulphonyl group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2$ group is replaced by a –NH-CO or –NH-NH group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2-CH_2$ group is replaced by a –NH-CO-NH, –NH-CO-O or $-O-CH_2-O$ group,

a C_{6-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2-CH_2-CH_2$ group is replaced by a $-NH-CH_2-CH_2-NH$, –NH-CO-CH_2-NH, $-NH-CH_2-CH_2-O$, –NH-CO-CH_2-O or $-O-CH_2-CH_2-O$ group,

a cycloheptyl-carbonylamino group wherein a $-CH_2-CH_2-CH_2-CH_2-CH_2$ group is replaced by a $-NH-CH_2-CH_2-CH_2-NH$, –NH-CO-CH_2-CH_2-NH, $-NH-CH_2-CH_2-CH_2-O$, –NH-CO-CH_2-CH_2-O or $-O-CH_2-CH_2-CH_2-O$ group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein one or two methylene groups are replaced by carbonyl groups,

a C_{4-7}-cycloalkenyl-carbonylamino or C_{4-7}-cycloalkenyl-C_{1-3}-alkyl-carbonylamino group,

a C_{3-7}-cycloalkyl-sulphonylamino, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-sulphonylamino, arylsulphonylamino or aryl-C_{1-3}-alkyl-sulphonylamino group or

a heteroarylcarbonylamino group,

while the imino groups contained in the above mentioned groups may be substituted independently of one another by a C_{1-3}-alkyl group,

and R^{11} denotes a hydrogen, fluorine, chlorine, bromine or iodine atom

or

a C_{1-3}-alkyl, C_{1-3}-alkyloxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy or cyano group,

R^2 denotes a hydrogen atom,

a C_{1-6}-alkyl group,

a C_{2-4}-alkenyl group,

a C_{3-4}-alkynyl group,

a C_{3-6}-cycloalkyl group,

a C_{3-6}-cycloalkyl-C_{1-3}-alkyl group,

a tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl or tetrahydropyranylmethyl group,

an aryl group,

an aryl-C_{1-4}-alkyl group,

an aryl-C_{2-3}-alkenyl group,

an arylcarbonyl-C_{1-2}-alkyl group,

a heteroaryl-C_{1-3}-alkyl group,

a furanylcarbonylmethyl, thienylcarbonylmethyl, thiazolylcarbonylmethyl or pyridylcarbonylmethyl group,

a C_{1-4}-alkyl-carbonyl-C_{1-2}-alkyl group,

a C_{3-6}-cycloalkyl-carbonyl-C_{1-2}-alkyl group,

an aryl-D-C_{1-3}-alkyl group, while D denotes an oxygen or sulphur atom, an imino, C_{1-3}-alkylimino, sulphinyl or sulphonyl group,

a C_{1-4}-alkyl group substituted by a group R_a, where

R_a denotes a cyano, carboxy, C_{1-3}-alkyloxy-carbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, di-(C_{1-3}-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

or a C_{2-4}-alkyl group substituted by a group R_b, where

R_b denotes a hydroxy, C_{1-3}-alkyloxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl or 4-ethyl-piperazin-1-yl group and is isolated from the cyclic nitrogen atom in the 3 position of the xanthine skeleton by at least two carbon atoms,

R^3 denotes a C_{3-8}-alkyl group,

a C_{1-3}-alkyl group substituted by a group R_c, where

R_c denotes a C_{3-7}-cycloalkyl group optionally substituted by one or two C_{1-3}-alkyl groups,

a C_{5-7}-cycloalkenyl group optionally substituted by one or two C_{1-3}-alkyl groups,

an aryl group or

a furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl-, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl group, while the above mentioned heterocyclic groups may each be substituted by one or two C_{1-3}-alkyl groups or by a fluorine, chlorine, bromine or iodine atom or by a trifluoromethyl, cyano or C_{1-3}-alkyloxy group,

a C_{3-8}-alkenyl group,

a C_{3-6}-alkenyl group substituted by a fluorine, chlorine or bromine atom, or a trifluoromethyl group,

a C_{3-8}-alkynyl group,

an aryl group or

an aryl-C_{2-4}-alkenyl group,

and

R^4 denotes an azetidin-1-yl or pyrrolidin-1-yl group which is substituted in the 3 position by an amino, C_{1-3}-alkylamino or a di-(C_{1-3}-alkyl)amino group and may additionally be substituted by one or two C_{1-3}-alkyl groups,

a piperidin-1-yl or hexahydroazepin-1-yl group which is substituted in the 3 position or 4 position by an amino, C_{1-3}-alkylamino or a di-(C_{1-3}-alkyl)amino group and may additionally be substituted by one or two C_{1-3}-alkyl groups,

a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl moiety is additionally substituted by an aminocarbonyl, C_{1-2}-alkyl-aminocarbonyl, di-(C_{1-2}-alkyl)aminocarbonyl, pyrrolidin-1-yl-carbonyl, (2-cyano-pyrrolidin-1-yl)-carbonyl, thiazolidin-3-yl-carbonyl, (4-cyano-thiazolidin-3-yl)carbonyl, piperidin-1-ylcarbonyl or morpholin-4-ylcarbonyl group,

a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl moiety is additionally substituted in the 4 position or 5 position by a hydroxy or methoxy group,

a 3-amino-piperidin-1-yl group wherein the methylene group in the 2 position or 6 position is replaced by a carbonyl group,

a piperidin-1-yl or hexahydroazepin-1-yl group substituted in the 3 position by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, wherein in each case

two hydrogen atoms on the carbon skeleton of the piperidin-1-yl or hexahydroazepin-1-yl group are replaced by a straight-chain alkylene bridge, this bridge containing 2 to 5 carbon atoms if the two hydrogen atoms are on the same carbon atom, or 1 to 4 carbon atoms if the hydrogen atoms are on adjacent carbon atoms, or 1 to 4 carbon atoms if the hydrogen atoms are on carbon atoms which are separated by one atom, or 1 to 3 carbon atoms if the hydrogen atoms are on carbon atoms which are separated by two atoms,

an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl or hexahydroazepin-1-yl group which is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a piperazin-1-yl or [1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two C_{1-3}-alkyl groups,

a 3-imino-piperazin-1-yl, 3-imino-[1,4]diazepan-1-yl or 5-imino-[1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two C_{1-3}-alkyl groups,

a [1,4]diazepan-1-yl group optionally substituted by one or two C_{1-3}-alkyl groups which is substituted in the 6 position by an amino group,

a C_{3-7}-cycloalkyl group which is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkyl group which is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a C_{3-7}-cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, while the two nitrogen atoms on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

an N-(C_{3-7}-cycloalkyl)-N-(C_{1-3}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, while the two nitrogen atoms on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

a C_{3-7}-cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

an N-(C_{3-7}-cycloalkyl)-N-(C_{1-3}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an N-(C_{3-7}-cycloalkyl-C_{1-2}-alkyl)-N-(C_{1-2}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

an N-(C_{3-7}-cycloalkyl-C_{1-2}-alkyl)-N-(C_{1-2}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

an R^{19}-C_{2-4}-alkylamino group wherein R^{19} is separated from the nitrogen atom of the C_{2-4}-alkylamino moiety by at least two carbon atoms and

R^{19} denotes an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an R^{19}-C_{2-4}-alkylamino group wherein the nitrogen atom of the C_{2-4}-alkylamino moiety is substituted by a C_{1-3}-alkyl group and R^{19} is separated from the nitrogen atom of the C_{2-4}-alkylamino moiety by at least two carbon atoms, where R^{19} is as hereinbefore defined,

an amino group substituted by the group R^{20} wherein

R^{20} denotes an azetidin-3-yl, azetidin-2-ylmethyl, azetidin-3-ylmethyl, pyrrolidin-3-yl, pyrrolidin-2-ylmethyl, pyrrolidin-3-ylmethyl, piperidin-3-yl, piperidin-4-yl, piperidin-2-ylmethyl, piperidin-3-ylmethyl or piperidin-4-ylmethyl group, while the groups mentioned for R^{20} may each be substituted by one or two C_{1-3}-alkyl groups,

an amino group substituted by the group R^{20} and a C_{1-3}-alkyl group wherein R^{20} is as hereinbefore defined, while the groups mentioned for R^{20} may each be substituted by one or two C_{1-3}-alkyl groups,

an R^{19}-C_{3-4}-alkyl group wherein the C_{3-4}-alkyl moiety is straight-chained and may additionally be substituted by one or two C_{1-3}-alkyl groups, where R^{19} is as hereinbefore defined,

a 3-amino-2-oxo-piperidin-5-yl or 3-amino-2-oxo-1-methyl-piperidin-5-yl group,

a pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, hexahydroazepin-3-yl or hexahydroazepin-4-yl group which is substituted in the 1 position by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)amino group,

or an azetidin-2-yl-C_{1-2}-alkyl, azetidin-3-yl-C_{1-2}-alkyl, pyrrolidin-2-yl-C_{1-2}-alkyl, pyrrolidin-3-yl, pyrrolidin-3-yl-C_{1-2}-alkyl, piperidin-2-yl-C_{1-2}-alkyl, piperidin-3-yl,

piperidin-3-yl-C_{1-2}-alkyl, piperidin-4-yl or piperidin-4-yl-C_{1-2}-alkyl group, while the abovementioned groups may each be substituted by one or two C_{1-3}-alkyl groups,

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, which may be mono- or disubstituted by R_h independently of one another, where the substituents are identical or different and R_h denotes a fluorine, chlorine, bromine or iodine atom, a trifluoromethyl, cyano, nitro, amino, aminocarbonyl, aminosulphonyl, methylsulphonyl, acetylamino, methylsulphonylamino, C_{1-3}-alkyl, cyclopropyl, ethenyl, ethynyl, hydroxy, C_{1-3}-alkyloxy, difluoromethoxy or trifluoromethoxy group,

by the heteroaryl groups mentioned in the definitions of the above mentioned groups are meant a pyrrolyl, furanyl, thienyl, pyridyl, indolyl, benzofuranyl, benzothiophenyl, quinolinyl or isoquinolinyl group,

or a pyrrolyl, furanyl, thienyl or pyridyl group wherein one or two methyne groups are replaced by nitrogen atoms,

or an indolyl, benzofuranyl, benzothiophenyl, quinolinyl or isoquinolinyl group wherein one to three methyne groups are replaced by nitrogen atoms,

or a 1,2-dihydro-2-oxo-pyridinyl, 1,4-dihydro-4-oxo-pyridinyl, 2,3-dihydro-3-oxo-pyridazinyl, 1,2,3,6-tetrahydro-3,6-dioxo-pyridazinyl, 1,2-dihydro-2-oxo-pyrimidinyl, 3,4-dihydro-4-oxo-pyrimidinyl, 1,2,3,4-tetrahydro-2,4-dioxo-pyrimidinyl, 1,2-dihydro-2-oxo-pyrazinyl, 1,2,3,4-tetrahydro-2,3-dioxo-pyrazinyl, 2,3-dihydro-2-oxo-indolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-oxo-1*H*-benzimidazolyl, 2,3-dihydro-2-oxo-benzoxazolyl, 1,2-dihydro-2-oxo-quinolinyl, 1,4-dihydro-4-oxo-quinolinyl, 1,2-dihydro-1-oxo-isoquinolinyl, 1,4-dihydro-4-oxo-cinnolinyl, 1,2-dihydro-2-oxo-quinazolinyl, 3,4-dihydro-4-oxo-quinazolinyl, 1,2,3,4-tetrahydro-2,4-dioxo-quinazolinyl, 1,2-dihydro-2-oxoquinoxalinyl, 1,2,3,4-tetrahydro-2,3-dioxo-quinoxalinyl, 1,2-dihydro-1-oxo-phthalazinyl, 1,2,3,4-tetrahydro-1,4-dioxo-phthalazinyl, chromanyl, cumarinyl,

2,3-dihydro-benzo[1,4]dioxinyl or 3,4-dihydro-3-oxo-2*H*-benzo[1,4]oxazinyl group,

and the above mentioned heteroaryl groups may be mono- or disubstituted by R_h, while the substituents may be identical or different and R_h is as hereinbefore defined,

and, unless otherwise stated, the above mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof, the prodrugs thereof and the salts thereof.

2. Compounds of general formula I according to claim 1, wherein

R^1, R^2 and R^3 are defined as in claim 1 and

R^4 denotes a pyrrolidin-1-yl group which is substituted in the 3 position by an amino group,

a piperidin-1-yl group which is substituted in the 3 position by an amino group,

a hexahydroazepin-1-yl group which is substituted in the 3 position or 4 position by an amino group,

a (2-aminocyclohexyl)amino group,

a cyclohexyl group which is substituted in the 3 position by an amino group, or

an N-(2-aminoethyl)-methylamino or an N-(2-aminoethyl)-ethylamino group,

while, unless otherwise stated, the above mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and salts thereof.

3. Compounds of general formula I according to claim 2, wherein

R^1 denotes a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by R^{10}, while

R^{10} denotes a formylamino group,

a C_{3-7}-cycloalkyl-carbonylamino or C_{3-7}-cycloalkyl-C_{1-3}-alkyl-carbonylamino group,

a C_{6-9}-bicycloalkyl-carbonylamino group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein

a methylene group is replaced by an oxygen or sulphur atom or by an imino, sulphinyl or sulphonyl group,

a (1,3-dioxolanyl)-carbonylamino, (1,4-dioxanyl)-carbonylamino, morpholin-2-yl-carbonylamino, morpholin-3-ylcarbonylamino or piperazin-2-yl-carbonylamino group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2$ group is replaced by an –NH-CO group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a $-CH_2-CH_2-CH_2$ group is replaced by an –NH-CO-O group,

a C_{5-7}-cycloalkyl-carbonylamino group wherein a methylene group is replaced by a carbonyl group,

a C_{5-7}-cycloalkenyl-carbonylamino or C_{5-7}-cycloalkenyl-C_{1-3}-alkyl-carbonylamino group,

a C_{3-7}-cycloalkyl-sulphonylamino, phenylsulphonylamino or phenyl-C_{1-3}-alkyl-sulphonylamino group or

a pyridinylcarbonylamino group,

R^2 denotes a hydrogen atom,

or a C_{1-3}-alkyl group,

R^3 denotes a C_{4-6}-alkenyl group,

a 2-butyn-1-yl group or

a 1-cyclopenten-1-yl-methyl group

and

R^4 denotes a piperidin-1-yl group which is substituted in the 3 position by an amino group,

a hexahydroazepin-1-yl group which is substituted in the 3 position or 4 position by an amino group,

a (2-aminocyclohexyl)amino group,

a cyclohexyl group which is substituted in the 3 position by an amino group, or

an N-(2-aminoethyl)-methylamino or an N-(2-aminoethyl)-ethylamino group,

while, unless otherwise stated, the above mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

4. Compounds of general formula I according to claim 3, wherein

R^1 denotes a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by a formylamino, pyridinylcarbonylamino or cyclopropylcarbonylamino group,

R^2 denotes a methyl group,

R^3 denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group or

a 2-butyn-1-yl group

and

R^4 denotes a (3-amino-piperidin-1-yl) group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

5. Compounds of general formula I according to claim 4, wherein

R^1 denotes a [2-(cyclopropylcarbonylamino)-phenyl]-carbonylmethyl or [2-(pyridylcarbonylamino)-phenyl]-carbonylmethyl group,

R^2 denotes a methyl group,

R^3 denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group or

a 2-butyn-1-yl group

and

R^4 denotes a (3-amino-piperidin-1-yl) group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

6. The following compounds of general formula I according to claim 1:

(1) 1-[2-(2-formylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

(2) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

(3) 1-[2-(2-formylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

(4) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-((E)-2-buten-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,

(5) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-((E)-2-buten-1-yl)-8-((*S*)-3-amino-piperidin-1-yl)-xanthine,

(6) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,

(7) 1-(2-{2-[(cyclopropylcarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-((*S*)-3-amino-piperidin-1-yl)-xanthine and

(8) 1-[2-(2-{[(pyridin-2-yl)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

as well as the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

7. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 6 with inorganic or organic acids or bases.

8. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 6 or a physiologically acceptable salt according to claim 7 optionally together with one or more inert carriers and/or diluents.

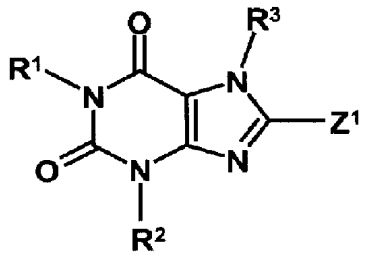
9. Use of a compound according to at least one of claims 1 to 7 for preparing a pharmaceutical composition which is suitable for treating type I and type II diabetes mellitus, arthritis, obesity, allograft transplantation and calcitonin-induced osteoporosis.

10. Process for preparing a pharmaceutical composition according to claim 8, characterised in that a compound according to at least one of claims 1 to 7 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

11. Process for preparing the compounds of general formula I according to claims 1 to 7, characterised in that

a) in order to prepare compounds of general formula I wherein R^4 is one of the groups mentioned in claim 1 linked to the xanthine skeleton via a nitrogen atom:

a compound of general formula



(II),

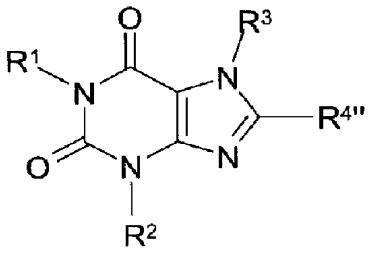
wherein

R^1 to R^3 are defined as in claim 1 and

Z^1 denotes a leaving group such as a halogen atom, a substituted hydroxy, mercapto, sulphinyl, sulphonyl or sulphonyloxy group,

is reacted with an amine of general formula $R^{4'}$-H, wherein $R^{4'}$ denotes one of the groups mentioned for R^4 in claim 1 which is linked to the xanthine skeleton via a nitrogen atom, or

b) a compound of general formula



(III),

wherein R^1, R^2 and R^3 are defined as in claim 1 and

$R^{4''}$ denotes one of the groups mentioned for R^4 hereinbefore which contain an imino, amino or alkylamino group, while the imino, amino or alkylamino group is substituted by a protective group, is deprotected, and is subsequently optionally alkylated at the imino, amino or C_{1-3}-alkylamino group, and/or

subsequently, if desired, any protecting groups used during the reaction are cleaved and/or

the compounds of general formula I thus obtained are resolved into their enantiomers or diastereomers and/or

the compounds of formula I thus obtained are converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids or bases.